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EXAMINER	
TRAN, MY CHAU T	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 11/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/091,240	SHAIR ET AL.	
	Examiner	Art Unit	
	MY-CHAU T. TRAN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,4,6-15,25-29,32,33,48,49,54-56,58-66 and 68* is/are pending in the application.

4a) Of the above claim(s) *8,11-15,25,27-29,56 and 58-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,4,6,7,9,10,16-24,26,32,33,48,49,54-56 and 68* is/are rejected.

7)☒ Claim(s) *55* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/29/2005 has been entered.

Application and Claims Status

2. Applicant's amendment and response filed 09/29/2005 is acknowledged and entered. Claims 2, 5, 16-24, 30, 31, 50-53, 57, and 67 have been cancelled. Claims 3, 4, 6-8, 10-15, 25-29, 32, 48, 54, 55, 58-64, and 68 have been amended.

3. In addition, the amendment filed includes claims with improper status identifiers. See 37 CFR 1.121 and MPEP § 714. For examples, claims 58-66 are withdrawn claims, yet applicant identifies these claims as "currently amended". These claims were withdrawn from further consideration as being drawn to nonelected species in the Office Action mailed on 13/28/2005. Appropriate correction is required.

4. The amendment filed on 12/14/2004: cancelled claims 1 and 34-47; amended claims 3, 7, 9, and 32; and added claims 48-68.

5. Claims 3, 4, 6-15, 25-29, 32, 33, 48, 49, 54-56, 58-66, and 68 are pending.

Election/Restrictions

6. Applicant has elected the following species for the elected invention (Claims 3, 4, 6-15, 25-29, 32-33, 48, 49, 54-56, 58-66, and 68) in the reply filed on 6/24/2003 and 6/7/2004:

a. A species of test compound. Applicant elected small molecule, which is Taxol.

b. A species of molecular sensor. Applicant elected 2,3-diaminonaphthalene (DAN), which is attached to the solid support via an amide bond shown in figure 4.

c. A species of decoding tag. Applicant elected inert halogenated compound.

d. A species of inducible reporter gene. Applicant elected nitric oxide synthase.

e. A species of reporter gene product. Applicant elected nitric oxide.

f. A species of chemical compound. Applicant elected nitric oxide.

g. A species of cell. Applicant elected yeast.

h. A species of solid support. Applicant elected solid phase resin beads (e.g., aminomethyl-TENTAGEL resin).

7. Claims 8, 11-15, 25, 27-29, 56, and 58-67 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to ***nonelected species***, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6/24/2003 and 6/7/2004.

8. Claims 3, 4, 6, 7, 9, 10, 16-24, 26, 32, 33, 48, 49, 54, 55, and 68 are under consideration in this Office Action.

Priority

9. This instant application claims benefit to a provisional application of 60/273,736 filed 03/05/2001. This instant application is granted the benefit of priority for 60/273,736 under 35 U.S.C 119(e).

Claim Objections

10. Claim 55 is objected to because of the following informalities:

The claimed limitation of "*wherein nitric oxide is detected by the detecting agent*" is synonymous with the claimed method step of "*identifying test compounds which promote or inhibit a biological event based on detection of nitric oxide by the detecting agent*". Thus, the claimed limitation of "*wherein nitric oxide is detected by the detecting agent*" is redundant with regard to the claimed method step of "*identifying test compounds which promote or inhibit a biological event based on detection of nitric oxide by the detecting agent*".

Appropriate correction is required.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 10, 48, 49, and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stylli et al. (US Patent 5,985,214) and Nakatsubo et al. (*Biol. Pharm. Bull.*, **1998**, 21(12), pgs. 1247-1250).

The instant invention recites a method of identifying a test compound that affects a biological event of interest. The method comprises the steps of: 1) providing a plurality of test compounds; 2) providing cells containing an inducible reporter gene, wherein expression of the reporter gene results in the production of nitric oxide in response to occurrence or non-occurrence of selected biological event; 3) contacting the cells with the plurality of test compounds; and 4) identifying test compounds which promote or inhibit a biological event based on production of nitric oxide.

Stylli et al. teaches an automated method and system for identifying chemicals having useful activity such as biological activities of chemicals and collecting informations resulting from such a process (e.g. see Abstract; col. 2, lines 35-41; col. 6, lines 1-24). The method comprise of testing a therapeutic chemical for modulating activity of a target in a cell-based assay (e.g. see col. 38, lines 46-67; col. 39, lines 1-9; col. 43, lines 6-9). The method comprises dispensing the reagents (compounds) into the addressable sample wells, which contains a predetermined volume of the sample (test cells) (e.g. see col. 6, lines 25-40; col. 8, lines 14-18).

Additionally, Stylli et al. disclose the method of dispensing live cell cultures into the sample wells (e.g. see col. 59, lines 20-32). The wells include formats such as 96 wells, 384 wells, or greater (e.g. see col. 15, lines 14-22). Stylli et al. disclose that various different cell-based assay can be employed with its systems wherein the assays include cell surface proteins (e.g. see col. 38, lines 46-47; col. 39, lines 1-9) and also various method of detection of the compound interaction with the target includes fluorescent measurement (e.g. see col. 27, lines 29-35; col. 28, lines 15-17; col. 39, lines 1-67 thru col. 42, lines 1-23). The compounds tested include combinatorial compounds (e.g. see col. 43, lines 21-44).

The method of Stylli et al. differs from the presently claimed invention by failing to disclose using a nitric oxide sensor for detecting NO synthase activity in a cell based assay that screens compounds for a characteristic of interest such as physiological or biological activity.

Nakatsubo et al. disclose a detection method for nitric oxide (NO) in living cells and tissue culture systems for NO synthase inhibitors using fluorometric determination with 2,3-diaminonapthalene (DAN)(see e.g. Abstract; pg. 1247, left col., line 36 thru right col., line 7; pg. 1248, right col., lines 18-37; pg. 1249, right col., lines 2-14; pg. 1249, figs. 3 and 6). The method comprises screening five compounds that are derivatives of Ebselen's compounds for their NO synthase inhibitory activity in activated rat aortic smooth muscle cells, i.e. NO production determination, and measuring the fluorescence intensity change of DAN (see e.g. pg. 1247, right col., lines 8-16; pg. 1248, left col., line 52 thru right col., line 6; pg. 1249, right col., lines 2-14; pg. 1249, figs. 3 and 6).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to disclose using a nitric oxide sensor for detecting NO synthase activity in a

cell based assay that screens compounds for a characteristic of interest such as physiological or biological activity as taught by Nakatsubo et al. in the method of Stylli et al. One of ordinary skill in the art would have been motivated to disclose using a nitric oxide sensor for detecting NO synthase activity in a cell based assay that screens compounds for a characteristic of interest such as physiological or biological activity in the method of Stylli et al. for the advantage of providing a simple yet sensitive fluorometric determination of NO synthase activity in a 96-well plate format (Nakatsubo: pg. 1249, right col., lines 15-20) since Stylli et al. disclose that any type of cell-base assay can be employed with system of Stylli et al. (e.g. see col. 38, lines 46-47; col. 39, line 60 to col. 40, line 50; col. 42, line 10-15). Thus any type of cell-base assay methodologies can be use in the system of Stylli et al. and the type of cell-base assay use would be a choice of experimental design and is considered within the purview of the cited prior art. Furthermore, one of ordinary skill in the art would have a reasonable expectation of success in the combination of Stylli et al. and Nakatsubo et al. because Nakatsubo et al. shown the success of using 2,3-diaminonapthalene (DAN) for detecting NO synthase activity in a cell based assay (see e.g. pg. 1249, right col., lines 2-14; pg. 1249, fig. 6).

Thus, the combine teachings of Stylli et al. and Nakatsubo et al. do render the method of the instant claims *prima facie* obvious.

14. Claims 3, 4, 6, 7, 9, 10, 16-24, 32, 33, 48, 49, 54, and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Still et al. (US Patent 5,565,324) and Misko et al. (*Analytical Biochemistry*, **1993**, 214(1), pgs. 11-16).

The instant invention recites a method of identifying a test compound that affects a biological event of interest. The method comprises the steps of: 1) providing a plurality of test

compounds; 2) providing cells containing an inducible reporter gene, wherein expression of the reporter gene results in the production of nitric oxide in response to occurrence or non-occurrence of selected biological event; 3) contacting the cells with the plurality of test compounds; and 4) identifying test compounds which promote or inhibit a biological event based on production of nitric oxide.

Still et al. teach methods and composition for encoding combinatorial chemistry (see e.g. Abstract; col. 3, lines 6-45). The methods includes the combinatorial synthesis that employs definable beads upon, which reactions are performed and to which the identifiers are bound, the method of screening the beads carrying the final product compounds for a characteristic of interest such as physiological or biological activity, and the method of analyzing the identifier tags attached to the solid supports for the reaction history of the final product compounds (see e.g. col. 3, lines 39-45; col. 5, lines 34-64; col. 29, line 65 to col. 30, line 51; col. 32, lines 14-22). The screening method comprises the steps of: 1) providing a plurality beads carrying the final product compounds (refers to instant claims 10, and 54; and instant claimed step 1) (see e.g. col. 30, lines 1-6); 2) providing cells wherein binding a surface membrane protein (refers to instant claimed reporter gene) produces an observable product (refers to instant claimed reporter gene product) that is expressed (refers to instant claim 18 and instant claimed step 2) (see e.g. col. 30, lines 32-42); 3) the final product compounds is detach from the bead in order to react with the cells (see e.g. col. 30, lines 13-15); 4) identifying the final product compounds that cause the expression of the observable product (refers to instant claimed step 3)(see e.g. col. 30, lines 42-44; col. 32, lines 14-22). The final product compounds are attached to the beads via a cleavable linker that can be cleave by irradiation with light (refers to instant claims 3-4) or chemical reagent such as thiol (refers to instant claim 68)(see e.g. col. 13, lines 44-64). Additionally, the Still et al. also disclosed other type of detachment method such as using

chemical reagent, and that the type of detachment method would depend on the type of linker use to attach the product to the bead (see e.g. col. 11, lines 29-64; col. 13, lines 44-64). Furthermore, the identifier tag attached to the solid supports is analyzed for the reaction history of the final product compounds (refers to instant claim 33) (see e.g. col. 6, lines 18-55; col. 26, lines 57-62; col. 32, lines 14-22).

The method of Still et al. differs from the presently claimed invention by failing to include using a nitric oxide (NO) molecular sensor for detecting NO synthase activity in a cell based assay that screens compounds for a characteristic of interest such as physiological or biological activity and that the nitric oxide molecular sensor is 2,3-diaminonapthalene (DAN).

Misko et al. disclose a cell-based assay for monitoring NO synthase activity using 2,3-diaminonapthalene (DAN) (see e.g. Abstract; pg. 12, left col., line 6-28; pg. 12, right col., line 32 thru pg. 13, left col., line 19; pg. 13, left col., line 25 to right col., line 10; pg. 15, right col., line 12 to pg. 16, left col., line 17; pg. 15, fig. 5). Although Misko et al. disclose measuring nitrite and quantify nitrite/nitrate level in serum or plasma, this type of measurement and quantification provides a useful method of indirectly estimating endogenously produced nitric oxide (NO) since direct measurement of NO in vivo is difficult due to its short half life and NO rapidly decomposes into stable end products nitrile and nitrate as evidenced by Rao et al. (*Brain Research*, **1998**, 793(1-2), pgs. 265-270)(see e.g. pg. 265, right col., lines 3-7). Thus, the method of Misko et al. does detect NO produced by NO synthase activity in a cell-based assay. This method provides a simple yet sensitive fluorometric determination of NO synthase activity in a 96-well plate format (pg. 11, right col., lines 27-35).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include the use of a nitric oxide molecular sensor for detecting NO synthase activity in a cell based assay that screens compounds for a characteristic of interest such as physiological or biological activity and the nitric oxide molecular sensor is 2,3-diaminonapthalene (DAN) as taught by Misko et al. in the method of Still et al. One of ordinary skill in the art would have been motivated to include the use of a nitric oxide molecular sensor for detecting NO synthase activity in a cell based assay that screens compounds for a characteristic of interest such as physiological or biological activity and the nitric oxide molecular sensor is 2,3-diaminonapthalene (DAN) in the method of Still et al. for the advantage of providing a simple yet sensitive fluorometric determination of NO synthase activity in a 96-well plate format (Misko: pg. 11, right col., lines 27-35). Furthermore, one of ordinary skill in the art would have reasonably expectation of success in the combination of Still et al. and Misko et al. because Misko et al. shown the success of using 2,3-diaminonapthalene (DAN) for detecting NO synthase activity in a cell based assay (Misko: pg. 13, left col., line 25 to pg. 14, right col., line 50).

Thus, the combine teachings of Still et al. and Misko et al. do render the method of the instant claims *prima facie* obvious.

15. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Still et al. (US Patent 5,565,324) and Misko et al. (*Analytical Biochemistry*, **1993**, 214(1), pgs. 11-16) as applied to claims 3, 4, 6, 7, 9, 10, 16-24, 32, 33, 48, 49, 54, and 68 above, and further in view of Ashby et al. (US Patent 5,569,588).

Still et al. teach methods and composition for encoding combinatorial chemistry (see e.g. Abstract; col. 3, lines 6-45). The methods includes the combinatorial synthesis that employs definable beads upon, which reactions are performed and to which the identifiers are bound, the method of screening the beads carrying the final product compounds for a characteristic of interest such as physiological or biological activity, and the method of analyzing the identifier tags attached to the solid supports for the reaction history of the final product compounds (see e.g. col. 3, lines 39-45; col. 5, lines 34-64; col. 29, line 65 to col. 30, line 51; col. 32, lines 14-22). The screening method comprises the steps of: 1) providing a plurality beads carrying the final product compounds (refers to instant claims 10, and 54; and instant claimed step 1) (see e.g. col. 30, lines 1-6); 2) providing cells wherein binding a surface membrane protein (refers to instant claimed reporter gene) produces an observable product (refers to instant claimed reporter gene product) that is expressed (refers to instant claim 18 and instant claimed step 2) (see e.g. col. 30, lines 32-42); 3) the final product compounds is detach from the bead in order to react with the cells (see e.g. col. 30, lines 13-15); 4) identifying the final product compounds that cause the expression of the observable product (refers to instant claimed step 3)(see e.g. col. 30, lines 42-44; col. 32, lines 14-22). The final product compounds are attached to the beads via a cleavable linker that can be cleave by irradiation with light (refers to instant claims 3-4) or chemical reagent such as thiol (refers to instant claim 68)(see e.g. col. 13, lines 44-64). Additionally, the Still et al. also disclosed other type of detachment method such as using chemical reagent, and that the type of detachment method would depend on the type of linker use to attach the product to the bead (see e.g. col. 11, lines 29-64; col. 13, lines 44-64). Furthermore, the identifier tag attached to the solid supports is analyzed for the reaction history of the final

product compounds (refers to instant claim 33) (see e.g. col. 6, lines 18-55; col. 26, lines 57-62; col. 32, lines 14-22).

Misko et al. disclose a cell-based assay for monitoring NO synthase activity using 2,3-diaminonapthalene (DAN) (see e.g. Abstract; pg. 12, left col., line 6-28; pg. 12, right col., line 32 thru pg. 13, left col., line 19; pg. 13, left col., line 25 to right col., line 10; pg. 15, right col., line 12 to pg. 16, left col., line 17; pg. 15, fig. 5). Although Misko et al. disclose measuring nitrite and quantify nitrite/nitrate level in serum or plasma, this type of measurement and quantification provides a useful method of indirectly estimating endogenously produced nitric oxide (NO) since direct measurement of NO in vivo is difficult due to its short half life and NO rapidly decomposes into stable end products nitrile and nitrate as evidenced by Rao et al. (*Brain Research*, **1998**, 793(1-2), pgs. 265-270)(see e.g. pg. 265, right col., lines 3-7). Thus, the method of Misko et al. does detect NO produced by NO synthase activity in a cell-based assay. This method provides a simple yet sensitive fluorometric determination of NO synthase activity in a 96-well plate format (pg. 11, right col., lines 27-35).

The combine teachings of Still et al. and Misko et al. are obvious over the presently claimed invention since one of ordinary skill in the art would have been motivated to combine the teachings of Still et al. and Misko et al. for the advantage of providing a simple yet sensitive fluorometric determination of NO synthase activity in a 96-well plate format (Misko: pg. 11, right col., lines 27-35). However, the combination of Still et al. and Misko et al. differs from the presently claimed invention by failing to include using yeast cell in the method of screening compounds for a characteristic of interest such as physiological or biological activity.

Ashby et al. teach the methods and compositions for modeling the transcriptional responsiveness of an organism to a candidate drug (see e.g. Abstract; col. 1, lines 40-60). The methods comprise the step of: (a) detecting reporter gene product Signals from each of a plurality of different, separately isolated cells of a target organism, wherein each of said cells contains a recombinant construct comprising a reporter gene operatively linked to a different endogenous transcriptional regulatory element (e.g. promoter) of said target organism such that said transcriptional regulatory element regulates the expression of said reporter gene, wherein said plurality of cells comprises an ensemble of the transcriptional regulatory elements of said organism sufficient to model the transcriptional responsiveness of said organism to a drug; (b) contacting each said cell with a candidate drug; (c) detecting reporter gene product signals from each of said cells; (d) comparing said reporter gene product signals from each of said cells before and after contacting each of said cells with said candidate drug to obtain a drug response profile; wherein said drug response profile provides an estimate of the physiological specificity or biological interactions of said candidate drug (see e.g. Abstract; col. 1, lines 40-60; col. 6, line 51 to col. 8, line 27). The cells include yeast cells (see e.g. col. 2, lines 19-45).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include yeast cell in a cell-based assay for screening compounds for a characteristic of interest such as physiological or biological activity as taught by Ashby et al. in the method combination of Still et al. and Misko et al. One of ordinary skill in the art would have been motivated to include yeast cell in a cell-based assay for screening compounds for a characteristic of interest such as physiological or biological activity in the method o combination of Still et al. and Misko et al. for the advantage of model system to obtain preliminary

information on compound specificity in higher eukaryotes, such as human (Ashby: col. 2, lines 19-26). Additionally, both Still et al. and Ashby et al. disclose gene product signal expressed by the cells (Still: col. 30, lines 35-36; Ashby: col. 1, lines 42-43). Furthermore, one of ordinary skill in the art would have reasonably expectation of success in the combination of Still et al., Misko et al., and Ashby et al. because Ashby et al. disclose by example the method of determining the compound characteristic of interest such as physiological or biological activity using yeast cells (Ashby: col. 10, line 34 to col. 11, line 60).

Thus, the combine teachings of Still et al., Misko et al., and Ashby et al. do render the method of the instant claims *prima facie* obvious.

16. Claims 3, 4, 6, 7, 9, 10, 16-24, 32, 33, 48, 49, 54, and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Still et al. (US Patent 5,565,324) and Nakatsubo et al. (*Biol. Pharm. Bull.*, **1998**, 21(12), pgs. 1247-1250).

The instant invention recites a method of identifying a test compound that affects a biological event of interest. The method comprises the steps of: 1) providing a plurality of test compounds; 2) providing cells containing an inducible reporter gene, wherein expression of the reporter gene results in the production of nitric oxide in response to occurrence or non-occurrence of selected biological event; 3) contacting the cells with the plurality of test compounds; and 4) identifying test compounds which promote or inhibit a biological event based on production of nitric oxide.

Still et al. teach methods and composition for encoding combinatorial chemistry (see e.g. Abstract; col. 3, lines 6-45). The methods includes the combinatorial synthesis that employs definable beads upon, which reactions are performed and to which the identifiers are bound, the method of screening the beads carrying the final product compounds for a characteristic of interest such as physiological or biological activity, and the method of analyzing the identifier

tags attached to the solid supports for the reaction history of the final product compounds (see e.g. col. 3, lines 39-45; col. 5, lines 34-64; col. 29, line 65 to col. 30, line 51; col. 32, lines 14-22). The screening method comprises the steps of: 1) providing a plurality beads carrying the final product compounds (refers to instant claims 10, and 54; and instant claimed step 1) (see e.g. col. 30, lines 1-6); 2) providing cells wherein binding a surface membrane protein (refers to instant claimed reporter gene) produces an observable product (refers to instant claimed reporter gene product) that is expressed (refers to instant claim 18 and instant claimed step 2) (see e.g. col. 30, lines 32-42); 3) the final product compounds is detach from the bead in order to react with the cells (see e.g. col. 30, lines 13-15); 4) identifying the final product compounds that cause the expression of the observable product (refers to instant claimed step 3)(see e.g. col. 30, lines 42-44; col. 32, lines 14-22). The final product compounds are attached to the beads via a cleavable linker that can be cleave by irradiation with light (refers to instant claims 3-4) or chemical reagent such as thiol (refers to instant claim 68)(see e.g. col. 13, lines 44-64). Additionally, the Still et al. also disclosed other type of detachment method such as using chemical reagent, and that the type of detachment method would depend on the type of linker use to attach the product to the bead (see e.g. col. 11, lines 29-64; col. 13, lines 44-64). Furthermore, the identifier tag attached to the solid supports is analyzed for the reaction history of the final product compounds (refers to instant claim 33) (see e.g. col. 6, lines 18-55; col. 26, lines 57-62; col. 32, lines 14-22).

The method of Still et al. differs from the presently claimed invention by failing to include using a nitric oxide (NO) molecular sensor for detecting NO synthase activity in a cell

based assay that screens compounds for a characteristic of interest such as physiological or biological activity and that the nitric oxide molecular sensor is 2,3-diaminonapthalene (DAN).

Nakatsubo et al. disclose a detection method for nitric oxide (NO) in living cells and tissue culture systems for NO synthase inhibitors using fluorometric determination with 2,3-diaminonapthalene (DAN)(see e.g. Abstract; pg. 1247, left col., line 36 thru right col., line 7; pg. 1248, right col., lines 18-37; pg. 1249, right col., lines 2-14; pg. 1249, figs. 3 and 6). The method comprises screening five compounds that are derivatives of Ebselen's compounds for their NO synthase inhibitory activity in activated rat aortic smooth muscle cells, i.e. NO production determination, and measuring the fluorescence intensity change of DAN (see e.g. pg. 1247, right col., lines 8-16; pg. 1248, left col., line 52 thru right col., line 6; pg. 1249, right col., lines 2-14; pg. 1249, figs. 3 and 6).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include using a nitric oxide (NO) molecular sensor for detecting NO synthase activity in a cell based assay that screens compounds for a characteristic of interest such as physiological or biological activity as taught by Nakatsubo et al. in the method of Still et al. One of ordinary skill in the art would have been motivated to include using a nitric oxide (NO) molecular sensor for detecting NO synthase activity in a cell based assay that screens compounds for a characteristic of interest such as physiological or biological activity in the method of Still et al. for the advantage of providing a simple yet sensitive fluorometric determination of NO synthase activity in a 96-well plate format (Nakatsubo: pg. 1249, right col., lines 15-20) since both Still et al. and Nakatsubo et al. disclose the method of enzyme assays to determine inhibitors among the libraries of compounds (Still: col. 31, lines 24-38; Nakatsubo: pg. 1249,

right col., lines 2-14; fig. 6). Furthermore, one of ordinary skill in the art would have a reasonable expectation of success in the combination of Still et al. and Nakatsubo et al. because Nakatsubo et al. shown the success of using 2,3-diaminonapthalene (DAN) for detecting NO synthase activity in a cell based assay (see e.g. pg. 1249, right col., lines 2-14; pg. 1249, fig. 6).

Thus, the combine teachings of Still et al. and Nakatsubo et al. do render the method of the instant claims *prima facie* obvious.

17. Claims 55 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Still et al. (US Patent 5,565,324) and Nakatsubo et al. (*Biol. Pharm. Bull.*, **1998**, 21(12), pgs. 1247-1250).

The instant invention recites a method of identifying a test compound that affects a biological event of interest. The method comprises the steps of: 1) providing a plurality of test compounds associated with a plurality of solid supports wherein a detecting agent is associated with the solid support; 2) providing cells containing an inducible nitric oxide reporter gene, wherein expression of the reporter gene results in the production of nitric oxide in response to occurrence or non-occurrence of selected biological event; 3) releasing the test compounds from the solid support; 4) contacting the cells with the plurality of test compounds; and 5) identifying test compounds which promote or inhibit a biological event based on detection of nitric oxide by the detecting agent.

Still et al. teach methods and composition for encoding combinatorial chemistry (see e.g. Abstract; col. 3, lines 6-45). The methods includes the combinatorial synthesis that employs definable beads upon, which reactions are performed and to which the identifiers are bound, the method of screening the beads carrying the final product compounds for a characteristic of interest such as physiological or biological activity, and the method of analyzing the identifier tags attached to the solid supports for the reaction history of the final product compounds (see e.g. col. 3, lines 39-45; col. 5, lines 34-64; col. 29, line 65 to col. 30, line 51; col. 32, lines 14-

22). The screening method comprises the steps of: 1) providing a plurality beads carrying the final product compounds (refers to instant claimed step 1)(see e.g. col. 30, lines 1-6); 2) providing cells wherein binding a surface membrane protein (refers to instant claimed reporter gene) produces an observable product (refers to instant claimed reporter gene product) that is expressed (refers to instant claimed step 2)(see e.g. col. 30, lines 32-42); 3) the final product compounds is detach from the bead in order to react with the cells (refers to instant claimed step 3)(see e.g. col. 30, lines 13-15); 4) identifying the final product compounds that cause the expression of the observable product (refers to instant claimed step 4)(see e.g. col. 30, lines 13-21, and 42-44; col. 31, lines 24-38; col. 32, lines 14-22). Additionally, the final product compounds are attached to the beads via a cleavable linker that can be cleave by irradiation with light or chemical reagent such as thiol (see e.g. col. 13, lines 44-64), and that the type of detachment method would depend on the type of linker use to attach the product to the bead (see e.g. col. 11, lines 29-64; col. 13, lines 44-64). Furthermore, the identifier tag attached to the solid supports is analyzed for the reaction history of the final product compounds (see e.g. col. 6, lines 18-55; col. 26, lines 57-62; col. 32, lines 14-22).

The method of Still et al. differs from the presently claimed invention by failing to include using a nitric oxide (NO) molecular sensor for detecting NO synthase activity in a cell based assay that screens compounds for a characteristic of interest such as physiological or biological activity.

Nakatsubo et al. disclose a detection method for nitric oxide (NO) in living cells and tissue culture systems for NO synthase inhibitors using fluorometric determination with 2,3-diaminonapthalene (DAN)(see e.g. Abstract; pg. 1247, left col., line 36 thru right col., line 7; pg.

1248, right col., lines 18-37; pg. 1249, right col., lines 2-14; pg. 1249, figs. 3 and 6). The method comprises screening five compounds that are derivatives of Ebselen's compounds for their NO synthase inhibitory activity in activated rat aortic smooth muscle cells, i.e. NO production determination, and measuring the fluorescence intensity change of DAN (see e.g. pg. 1247, right col., lines 8-16; pg. 1248, left col., line 52 thru right col., line 6; pg. 1249, right col., lines 2-14; pg. 1249, figs. 3 and 6).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include using a nitric oxide (NO) molecular sensor for detecting NO synthase activity in a cell based assay that screens compounds for a characteristic of interest such as physiological or biological activity as taught by Nakatsubo et al. in the method of Still et al. One of ordinary skill in the art would have been motivated to include using a nitric oxide (NO) molecular sensor for detecting NO synthase activity in a cell based assay that screens compounds for a characteristic of interest such as physiological or biological activity in the method of Still et al. for the advantage of providing a simple yet sensitive fluorometric determination of NO synthase activity in a 96-well plate format (Nakatsubo: pg. 1249, right col., lines 15-20) since both Still et al. and Nakatsubo et al. disclose the method of enzyme assays to determine inhibitors among the libraries of compounds (Still: col. 31, lines 24-38; Nakatsubo: pg. 1249, right col., lines 2-14; fig. 6). Furthermore, one of ordinary skill in the art would have a reasonable expectation of success in the combination of Still et al. and Nakatsubo et al. because Nakatsubo et al. shown the success of using 2,3-diaminonapthalene (DAN) for detecting NO synthase activity in a cell based assay (see e.g. pg. 1249, right col., lines 2-14; pg. 1249, fig. 6).

Thus, the combine teachings of Still et al. and Nakatsubo et al. do render the method of the instant claims *prima facie* obvious.

Withdrawn Rejection(s)

18. The rejections of claims 2-7, 9-10, 18-20, 26, and 30-33 under 35 USC 112, first paragraph (written description) has been withdrawn in light of applicant's cancellation of claims 2, 5, 18-20, 30, and 31.

19. The rejections of claim 55 under 35 USC 112, first paragraph (written description) has been withdrawn in light of applicant's cancellation of claim 55.

20. The rejections of claim 68 under 35 USC 112, second paragraph, as being indefinite has been withdrawn in light of applicant's amendments of claim 68.

21. The rejection of claims 2, 10, 18-20, 26, 30, 31, and 54 under 35 USC 102(b) as being anticipated by Foulkes et al. (US Patent 5,580,722) has been withdrawn in light of applicant's amendments of claims 10, 26, and 54 and cancellation of claims 2, 5, 18-20, 30, and 31.

22. The rejection of claims 2-4, 10, 18, 26, and 54 under 35 USC 102(b) as being anticipated by Borchardt et al. (*Chemistry & Biology*, **1997**, 4(12), pgs. 961-968) has been withdrawn in light of applicant's amendments of claims 3, 4, 10, 26, and 54 and the cancellation of claims 2 and 18.

23. The rejection of claims 2-4, 10, 18, 33, and 54 under 35 USC 102(b) as being anticipated by Still et al. (US Patent 5,565,324) has been withdrawn in light of applicant's amendments of claims 3, 4, 10, 26, and 54 and cancellation of claims 2 and 18.

24. The rejection of claim 55 under 35 USC 102(b) as being anticipated by Still et al. (US Patent 5,565,324) has been withdrawn in light of applicant's amendments of claim 55.

25. The rejection of claims 2-4, 10, 18, 26, 33, 53, 54, and 68 under 35 USC 103(a) as being obvious over Still et al. (US Patent 5,565,324) and Ashby et al. (US Patent 5,569,588) has been withdrawn in view of applicant's amendments of claims 3, 4, 6-8, 10 and 54 and cancellation of claims 2, 5, 18-20, 30, 31, 53, and 57.

26. The rejection of claims 2-7, 9-10, 18-20, 30-31, 33, 53, 54, 57, and 68 under 35 USC 103(a) as being obvious over Still et al. (US Patent 5,565,324) and Misko et al. (*Analytical Biochemistry*, **1993**, 214(1), pgs. 11-16) has been withdrawn in view of applicant's amendments of claims 3, 4, 6-8, 10 and 54 and cancellation of claims 2, 5, 18-20, 30, 31, 53, and 57.

Response to Arguments

27. Applicant's argument directed to the rejection under 35 USC 103(a) as being unpatentable over Still et al. (US Patent 5,565,324) and Misko et al. (*Analytical Biochemistry*, **1993**, 214(1), pgs. 11-16) was considered but they are not persuasive for the following reasons.

Applicant contends that neither Still et al. nor Misko et al. teach the detection of nitric oxide, NO. Thus, the combine teachings of Still et al. and Misko et al. are not obvious over the presently claimed method.

Applicant's arguments are not convincing since the combine teachings of Still et al. and Misko et al. do render the method of the instant claims *prima facie* obvious.

It is the examiner positions that Misko et al. do teach the detection of nitric oxide, NO. Although Misko et al. disclose measuring nitrite and quantify nitrite/nitrate level in serum or plasma, this type of measurement and quantification provides a useful method of indirectly estimating endogenously produced nitric oxide (NO) since direct measurement of NO in vivo is difficult due to its short half life and NO rapidly decomposes into stable end products nitrile and nitrate as evidenced by Rao et al. (*Brain Research*, **1998**, 793(1-2), pgs. 265-270)(see e.g. pg. 265, right col., lines 3-7). Thus, the method of Misko et al. does detect NO produced by NO synthase activity in a cell-based assay.

Therefore, the combine teachings of Still et al. and Misko et al. do render the method of the instant claims *prima facie* obvious, and the rejection is maintained.

Conclusion

28. No Claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to My-Chau T. Tran whose telephone number is 571-272-0810.

The examiner can normally be reached on Monday: 8:00-2:30; Tuesday-Thursday: 7:30-5:00; Friday: 8:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

mct
November 27, 2005

PADMASHRI PONNALURI
PRIMARY EXAMINER